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Research Letter

Successful Management of Checkpoint Inhibitor-Induced Arthritis With Disease-Modifying Antirheumatic Drugs During Active Immune Checkpoint Inhibition Treatment

To the Editor:

Arthritis induced by immune checkpoint inhibitors (ICPi) has been reported to occur in 1% to 7% of ICPi-treated patients with cancer.[1-4] Treatment generally starts with glucocorticoids (GCs) before disease-modifying antirheumatic drugs (DMARDs) are considered.[5] No randomized treatment trials have been performed on wheather DMARD treatment is effective if given concurrently with ICPi treatment. There is a knowledge gap on the effectiveness of DMARD treatment to achieve remission of ICPi-induced arthritis when given concomitantly with ICPi treatment. Here we present 12 cases of patients treated for ICPi-induced arthritis with conventional synthetic and/or biologic DMARDs in our practice; 6 patients were treated concomitantly with DMARDs and ICPi, and 6 had stopped the ICPi treatment before the start of DMARDs. The aim is to compare the 2 groups for differences in frequency of arthritis remission after DMARD treatment.

This retrospective case series was conducted at the rheumatology clinic at Sahlgrenska University Hospital. We identified patients, referred to the clinic from September 2018 to August 2021, with a diagnosis of ICPi-induced arthritis requiring treatment with conventional or biologic DMARDs. All clinical aspects were confirmed by 2 designated rheumatologists. We excluded patients with a previous diagnosis of autoimmune disease. Clinical data were retrospectively collected at first visit to the rheumatologist and at all follow-up visits. Duration of ICPi (nivolumab, pembrolizumab, and ipilimumab) and DMARD (methotrexate [MTX], adalimumab [ADA], and tocilizumab [TCZ]) treatments were recorded along with the cumulative dose of systemic GCs. Remission of arthritis was defined as no swollen joints detected by the rheumatologist on clinical examination. End of follow-up was June 2022.

The study was approved by the regional ethics committee of Gothenburg (Dnr. 449-12 and 477-18). Patient written consent was not required in this retrospective, observational study according to the ethical permit.

The response to DMARD treatment is shown in Table 1. Six patients received concurrent ICPi and DMARDs (patients A-F) and 6 received DMARDs after ICPi treatment was stopped (patients G-L). The age range was 37 years to 81 years and 67% were male. All patients were negative for rheumatoid factor and anticyclic citrullinated peptide antibodies. Patients presented with monoarthritis (n = 1), oligoarthritis (n = 6), or polyarthritis (n = 5). The severity of arthritis was comparable between the groups shown by a similar duration of DMARD treatment (Table 1). In addition to DMARDs, 11 of 12 patients received systemic GCs (cumulative doses during active arthritis shown in Table 1) and 4 of 12 patients were given intraarticular GCs (patients A, E, H, and K).

All patients, except 1 (patient G), reached remission of arthritis after DMARD initiation, independently of ICPi treatment being continued or held; time to remission was 12 to 32 weeks in the group that continued ICPi treatment and 4 to 36 weeks in the group that discontinued ICPi. Five patients had combination therapy with MTX and ADA; of these, 1 patient (patient D) needed to switch from ADA to TCZ to achieve

Table 1. ICPi treatment status and response to DMARD treatment.

Patient	Time to Arthritis After ICPi Initiation, wks	ICPi Continued After DMARD Initiation	Time to Remission of Arthritis After DMARD Initiation, wks	Maximum No. of Swollen Joints	Cumulative GC Dose During Active Arthritis, mg	Time to GC Stop After DMARD Initiation, wks	Duration of DMARDs, mos	DMARDs
A	40	Yes	12	24	770	8	29 (ongoing)	MTX, ADA
B	119	Yes	20	2	3300	18	24	MTX, ADA
C	4	Yes	12	1	1085	8	9	MTX
D	10	Yes	32	38	180	4	19	MTX, ADA, TCZ
E	8	Yes	20	4	1425	24	17 (ongoing)	MTX
F	3	Yes	16	2	1500	12	7	MTX
G	23	No	Not in remission	4	0	No GCs	19 (ongoing)	MTX, ADA
H	62	No	36	5	3640	40	45 (ongoing)	MTX, ADA
I	24	No	4	12	625	10	12	MTX
J	7	No	10	4	225	8	14	ADA
K	17	No	16	3	2150	12	17	TCZ
L	25	No	12	7	5100	GCs not discontinued	12	ADA

ADA: adalimumab; DMARD: disease-modifying antirheumatic drug; GC: glucocorticoid; ICPi: immune checkpoint inhibitor; MTX: methotrexate; TCZ: tocilizumab.

remission. Cessation of ADA resulted in a relapse of symptoms for 1 patient from each group (patients A and H), despite ICPi treatment being stopped 9 months before for patient A and more than 2 years before for patient H. Both needed to restart ADA to achieve remission. In summary, the frequency of clinical remission was similar in patients who received DMARDs concurrently with ICPi vs those who had previously stopped ICPi treatment.

Most patients initially received systemic GCs as arthritis treatment but were treated with DMARDs as they did not achieve remission with corticosteroids alone. The fact that several patients had relapse in arthritis when DMARDs were tapered, but not when GCs were tapered, suggests that DMARDs were essential to keep the patients in remission. Data on malignancy and ICPi treatment are shown in Table 2. Patients G to L, who discontinued ICPi treatment before DMARD initiation, had shorter duration of ICPi treatment (range 2-18 months) compared to those who received ICPi and DMARDs concurrently (range 6-24 months).

The specific question of whether a similar remission rate of ICPi-induced arthritis after DMARD treatment can be expected independently of continued or discontinued ICPi treatment has not been clearly answered. MTX, tumor necrosis factor inhibitors (TNFi), and interleukin-6 receptor inhibitors have all been described as both effective and ineffective when used without disrupting ICPi treatment.[2,4,6-8] Kim et al described 1 patient in remission on TCZ, whereas Richter et al and De La Fuente et al described partial resolution of symptoms for 5 patients on the same treatment.[4,6,8] Calabrese et al and De La Fuente et al described 5 patients on various TNFi, with 2 of them showing significant improvement.[7,8] In an observational study of ICPi-induced arthritis, the duration of arthritis was similar regardless of continued ICPi treatment.[9] TNFi have been studied as a treatment for ICPi-induced colitis with good symptom control and without disrupting ICPi treatment regimen.[10]

Our small case series indicates that both conventional and biologic DMARDs can be used without holding ICPi treatment as all patients in this group reached remission. However, the results need to be replicated in a larger cohort before definite conclusions can be drawn. Moreover, both the effectiveness and safety of concurrent ICPi and DMARD treatment need to be studied in larger cohorts to find the optimal treatment strategy for arthritis remission, taking into account effects on malignancy.

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Table 2. ICPi treatment and tumor response.

Patient	Malignancy (Stage)	Tumor Response	ICPi	ICPi Duration, mos	Duration of Follow-Up[a], mos
A	MM (IV)	CR	Anti-PD-1 + anti-CTLA-4	24	48
B	MM (IV)	PR	Anti-PD-1 + anti-CTLA-4	24	65
C	MM (III)	Progress	Anti-PD-1	12	31
D	Head and neck (IV)	Progress	Anti-PD-1	18	28
E	MM (III)	Adjuvant without progress	Anti-PD-1	12	25
F	NSCLC (IV)	Progress	Anti-PD-1	6	13
G	MM (III)	CR	Anti-PD-1	9	34
H	MM (IV)	CR	Anti-PD-1	18	73
I	NSCLC (IV)	Progress	Anti-PD-1	7	46
J	MM (III)	Progress	Anti-PD-1	3	25
K	MM (III)	Progress	Anti-PD-1	5	38
L	MM (IV)	Progress	Anti-PD-1	2	13

[a]From ICPi start to end of follow-up. anti-CTLA-4: anticytotoxic T lymphocyte antigen 4; anti-PD-1: antiprogrammed cell death 1; CR: complete response; ICPi: immune checkpoint inhibitor; MM: malignant melanoma; NSCLC: nonsmall cell lung cancer; PR: partial response.

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